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ORIGINAL ARTICLE

Effect of Zinc Supplementation on Growth of Low Birth Weight Infants Aged 1–6 Mo in Ardabil, Iran

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Abstract
Objective To assess the effect of zinc supplementation on growth of low birth weight (LBW) infants aged 1–6 mo.
Methods LBW infants were enrolled at birth and randomly assigned to receive 5 mg elemental Zn per day (n=45) or placebo (n=45) until 6 mo of age. They were followed monthly for information on compliance; anthropometric measurements were performed monthly.
Results After randomization, 5 infants from zinc group and 9 from placebo group were excluded. At 6 mo of age, significantly greater weight gains were observed in the zinc than in the placebo group (4995±741g in zinc group *vs*. 3896±865 g in placebo group, $p=0.036$). Length gain during the study period improved in zinc group (16.9±8.2 cm *vs*. 15.1±4.1 cm, $p=0.039$); after zinc supplementation head circumference were increased (8.7±1.4 cm *vs*. 7.4±1.5 cm $p<0.001$). In male infants, total weight gain and height and head circumference gain were higher in the zinc than in the placebo group. However, only head circumference change was statistically significant. A similar trend was observed among female infants, but these differences were not statistically significant. There was no significant relation between breast-feeding status and the main outcome variables.
Conclusions Infants in the present study showed improvements in growth rate, but more studies are required in this field to confirm this fact.

Keywords Zinc supplementation · Infants · Growth · Iran

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Introduction

Zinc has been known as an essential trace element for humans and animals since the 1930s [1]. It has been documented that a sufficient intake of micronutrients is necessary for growth and development of children [2]. Zinc nutrition has received increasing attention because of the recently available evidence that its deficiency may have grave consequences in humans [3]. Marginal and moderate zinc deficiencies in children with impairment in their growth have been reported from developed and developing countries [4]. The effects of such a deficient state in humans can be harmful because zinc is essential for normal fetal growth and development, and it is necessary during the first years of life when the body is growing rapidly [5, 6]. There is a evidence that trace element deficiencies such as zinc, copper and magnesium during pregnancy play an important role on pregnancy outcome [7].

Intrauterine growth retardation, a consequence of zinc deficiency, increases the risk of morbidity and mortality of the newborn. Zinc is a metal with great nutritional importance and is particularly necessary in cellular replication and development of the immune response [8]. Therefore, if the growing fetus and infant are at risk of developing zinc deficiency, then an adequate supply of it is essential for normal growth [9].

Although zinc deficiency is associated with growth impairment, the benefits of zinc supplementation on incremental growth are controversial [10]. Most of the intervention trials studying the effect of zinc on growth or morbidity have been performed in children >6 mo of age, when the period of highest growth velocity has already passed. It was therefore hypothesized that earlier interventions might be more effective in preventing growth faltering and reducing morbidity patterns among children at risk [11]. Unfortunately, only limited information is available on the effect of zinc supplementation in younger infants, and the results are not conclusive. Beneficial effects on growth and morbidity were observed after zinc supplementation in among low birth weight (LBW <2,500 g) and small -for-gestational-age infants in Brazil [12] and Chile [13], respectively. However, in Bangladesh no effect of zinc supplementation on growth was observed in children <6 mo with normal serum zinc concentration, but zinc-deficient infants showed improvement in growth rate after zinc supplementation [14]. According to clinical evidence, low birth weight is one of the health problems and nutritionists believe zinc intake is inadequate in Ardabil city, northwest of Iran.

To investigate the effect of zinc supplementation on growth in low-birth-weight infants, an intervention trail was performed among 4 to 24-wk- old low birth weight infants in this area.

Material and Methods

The study was conducted in Ardabil city in northwest of Iran, from November 2002 through March 2005. The authors selected low weight birth infants from an educational hospital. The main outcome of interest was growth between 1 and 6 mo of life. A total of 90 subjects; 45 each in Zn and placebo group, were defined as maximum sample size that research department accepted to provide cost and support. A birth assessment form was completed and birth weight, length, and head circumference were recorded. Weight was measured with an electronic scale Tefal, France, by trained nurse. Only children with weight <2,500 g were considered for the study. Parents of the newborns who were low birth weight were invited to participate in the study. Inclusion criteria were singleton, birth weight <2,500 g, no evidence of congenital malformation or diseases that affect growth such as rubella, herpes, toxoplasmosis and syphilis, resident of urban area of Ardabil.

Before enrolment, a full explanation of the study was given to parents, and written informed consent was obtained. The study was approved by the medical ethics committee at the Ardabil University of Medical Sciences. Infants were randomly allocated to receive 5 ml/d of liquid with or without 5 mg elemental Zn (zinc sulphate). The framework of randomization was prepared by a research officer who was not involved in the study and who worked closely with the pharmacy. The method of randomization was permuted

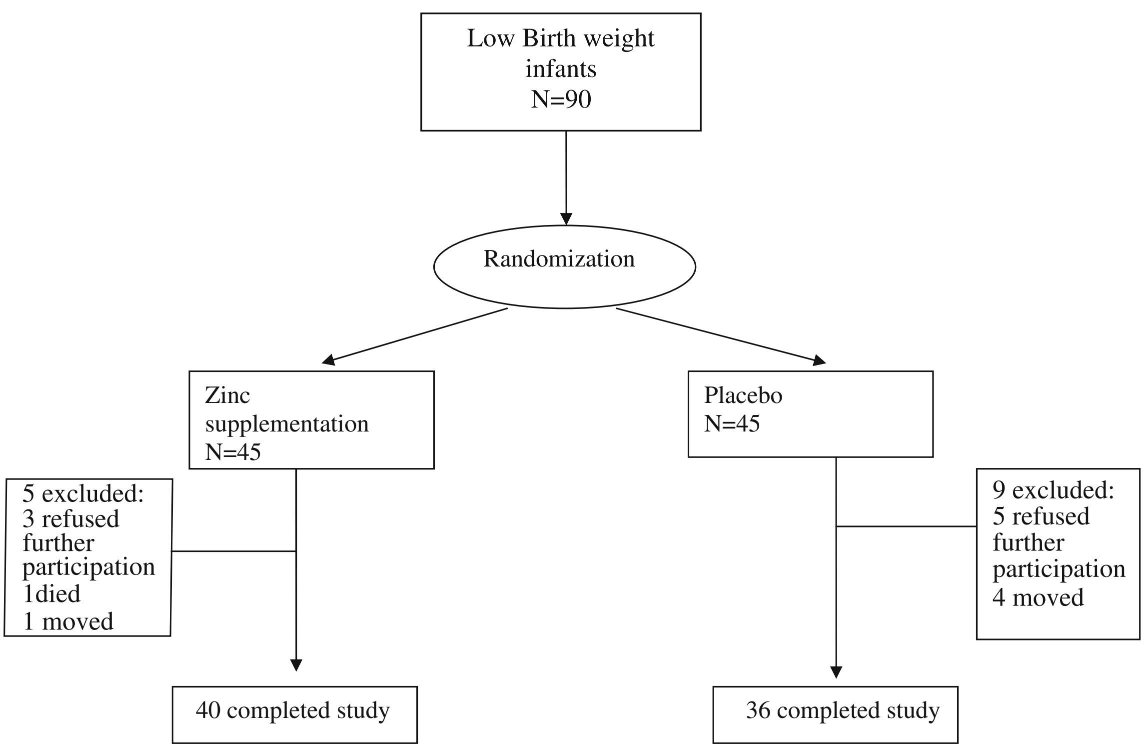

Fig. 1 Trial profile

Table 1 Characteristics of infants on admission to the study

Characteristic	Zinc-supplemented	Placebo
Sex(M/F)	28/17	20/25
Maternal age(y)	24.2±5.1	25.2±6.1
Paternal age(y)	28.3±5.6	29.3±5.7
Parity	1.5±0.8	1.7±0.9
Birth weight(g)	2109±439	2152±434
Length at birth(cm)	43.9±3.1	43.37±2.7
Head circumference(cm)	31.68±1.89	31.8±1.9
Gestational age	33.5±2.5	34.1±2.1
% of small for gestational age	11.9	10
% of prematurity	88	90

blocks; regarding two treatments A and B, 6 blocks of length 4 were chosen. Infants were allocated to treatment or placebo group in the order in each block. The selection of blocks continued until the sample size completed. Pharmacy prepared syrups that contained Zn + multivitamin and preservative and multivitamin and preservative only. The liquids were indistinguishable in both appearance and taste. They labelled each bottle with A or B as part of specific identification, however each bottle was provided with the name of each infant and date. The serial identification number given at enrolment was used to allocate a child to A or B groups and it was not identifiable by the research team and participants. The codes of the supplements were unknown to both the participants and study staff and were broken only after data editing.

The randomization process allocated enrolled infants to receive 5 ml of either zinc sulphate or placebo daily between 4 wk and 24 wk of age. When the neonate was 28 d old, the mother was given a bottle of the supplement or placebo and advised to start giving the syrup from 30 d of age; daily dose of 5 ml was given, one bottle was enough for 1 mo, and a general practitioner gave necessary explanation about the usage to the parents. The baseline information was collected on the home visit at 28 d of age, including socioeconomic indicators and family characteristics.

Each enrolled child was visited at home by trained interviewers every month from 1 mo to end of 6 mo. If the child was not available, a second visit was made with after 3 d.

Table 2 Changes in anthropometric indicators between 4 and 24 week

	Zinc group (μ ± SD)	Placebo group (μ ± SD)	p
Weight gain(g)	4295±741	3896±865	0.036
Length growth(cm)	16.85±3.2	15.07±4.1	0.039
Change in head circumference(cm)	8.68±1.39	7.43±1.51	0.001

Table 3 Anthropometrics indicators between 4 and 24 wk of age by sex for infants in the zinc and placebo groups

		Zinc group	Placebo group
Weight gain(g)	Male	4509±733	4146±977
	Female	3886±584	3717±749
Length gain(cm)	Male	17.2±3.4	15.6±4.99
	Female	16.1±2.9	14.7±3.3
Head circumference gain (cm)	Male	8.98±1.22	7.6±1.36
	Female	8.1±1.6	7.3±1.6

Anthropometric indicators were measured every month, and the pattern of feeding and other special conditions was recorded. Also the compliance with supplement consumption was checked.

Statistical Analysis

Statistical analysis was performed by using SPSS ver 11. Means were compared by using the analysis of variance test for repeated measurements. For simple comparison between 2 means, the authors used the student's *t* test. $p<0.05$ was taken as the limit of significance; all of results for continuous variables are expressed as mean ± standard deviation.

Results

After randomization was performed, 5 infants from the zinc supplementation (11.1%) group and 9 from the placebo group (20.9%) were excluded (1 infant died, 8 parents refused further participation, 5 infants moved) [Fig. 1].

Biodemographic characteristics of infants were similar at baseline (Table 1).

Feeding patterns had no significant differences between zinc and placebo groups. At 24^{th} wk of age, 63.6% of all the infants were exclusively breast-fed, the duration of exclusive breast-feeding was similar in zinc and placebo groups (5.2+1.5 *vs*. 4.8+1.7). 22.1% were partially breast-fed (breast milk and the complementary fluids or food) and 14.3% were on formula feeds. There was no significant relation between breast-feeding and formula feeding status at 1 or 6 mo of age and the main outcome variables.

After zinc supplementation, significantly greater changes in weight, length and head circumference were observed between 4 and 24 wk of age, for infants in the zinc and placebo groups (Table 2).

In male infants, total weight gain between 4 and 24 wk of age (4,509±733 g compared with 4,146±977 g in the zinc and placebo groups) was higher in the zinc group than in the placebo group. However, this difference was not statistically significant. A similar trend was observed for total length gain and head circumference but only the difference in head circumference was significant between zinc and placebo groups (8.98±1.22 compared with 7.6±1.36 p=0.002). Total weight gain, length and head circumference change between 4 and 24 wk of age were higher in the zinc group than in the placebo group among the female infants, but these differences were not statistically significant (Table 3).

Discussion

In the present study supplementation with 5 mg elemental Zn/d between 4 and 24 wk of age improved the growth of low birth-weight infants. It was observed that after supplementation, these infants had significantly greater weight gain, and improved length and head circumference. A study by Friel et al. in 1993 on Canadian low birth weight infants (preterm infants) was started at discharge from the hospital, 1 mo of age and continued until 12 mo of age. The study indicates a small but significantly greater height gain z-score over the study period; the effect is more significant in girls [15].

Osendarp et al. assessed the effect of zinc supplementation on growth and morbidity in poor Bangladeshi infants aged 4–24 wk. In their study, zinc supplementation improved growth rate in zinc deficient infants (<9.18 micro mol/L at baseline), but in other infants with serum zinc concentrations >9.18 micro mol/L, zinc supplementation improved only biomedical zinc status and no significant changes were observed in growth rate during the study time frame [14].

Castillo-Duran et al. performed a study on Chilean infants born small for gestational age, and found weight increments in the supplemented group were significantly higher than those in the placebo group at 2 mo. Length increments were also greater in zinc group than in the placebo group at 6 mo of age. Weight-for-length improved similarly in both groups. Significantly greater weight-for-age and length -for-age z-score gain are found in the supplemented group; but only in girls. This effect is evident in those who receive whole cow's milk but not in those who are breastfed [13].

Lira et al. performed a study on low birth weight full-term infants in north east Brazil; low birth weight full term infants were given daily either 5 mg Zn, 1 mg zinc or placebo during first 24 wk of age. They found no effect on any outcome with 1 mg zinc, but 5 mg zinc/d had effect on weight gain during 17–26 wk of-age [12].

In a study in India that assessed the impact of zinc supplementation on growth and morbidity of low birth weight infants, showed that zinc supplementation had a beneficial impact on weight gain among LBW infants [16]. Marta Diaz-Gomez et al. showed zinc supplementation has a positive effect on linear growth in premature infants [17]; in the present study most of the infants were premature.

Beneficial effect of breastfeeding on weight gain, especially in LBW infants has been amply demonstrated in the previous studies [16, 18]. The feeding pattern was similar in both the groups, hence the impact of zinc supplementation was supported by the protective action of breastfeeding. In addition, zinc requirements of low birth weight infants are high for reasons including: immature gastrointestinal tracts, and low body stores of zinc [19].

Conclusions

The present study showed that zinc supplementation between 4 and 24 wk of age has been effective in weight and length gain in low birth weight infants. However, these findings have to be supported by other large-scale studies in other parts of Iran and other developing countries, especially in areas with high incidence of LBW.

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Contributions AN: conducted the research design, data analysis and prepared first draft of the manuscript; BM: involved in infant visit as a specialist to prescribe zinc supplementation and monitoring the infants, and reviewed manuscript. SHSM: coordinator of the project and provided monthly visit to record measurements of growth and also involved in data entry and analysis and revised the final manuscript.

Conflict of Interest None.

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References

1. Nutrition classics. The American Journal of Physiology. Volume 107, 1934, pages 146–156. "Zinc in the nutrition of the rat" by W. R. Todd, C.A. Elvehjem and E.B. Hart. Nutr Rev. 1980;38:151–4
2. Singh M. Role of micronutrients for physical growth and mental development. Indian J Pediatr. 2004;71:59–62.
3. Bhatnagar S, Natchu UC. Zinc in child health and disease. Indian J Pediatr. 2004;71:991–5.
4. Hambidge M. Human zinc deficiency. J Nutr. 2000;130:1344S–9S. Review.
5. Fung EB, Ritchie LD, Woodhouse LR, Roehl R, King JC. Zinc absorption in women during pregnancy and lactation: a longitudinal study. Am J Clin Nutr. 1997;66:80–8.
6. Brown JL, Pollitt E. Malnutrition, poverty and intellectual development. Sci Am. 1996;274:38–43.

7. Pathak P, Kapil U. Role of trace elements zinc, copper and magnesium during pregnancy and its outcome. Indian J Pediatr. 2004;71:1003–5.
8. Valdes-Ramos R. Zinc: a prenatal point of view. Progr Food Nutr Sci. 1992;16:279–306.
9. Simmer K, Thompson RP. Zinc in the fetus and newborn. Acta Paediatr Scand Suppl. 1985;319:158–63.
10. Rosado JL. Separate and joint effects of micronutrient deficiencies on linear growth. J Nutr. 1999;129:531S–3S.
11. Hambidge KM. Zinc deficiency in young children. Am J Clin Nutr. 1997;65:160–1.
12. Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. Am J Clin Nutr. 1998;68:418S–24S.
13. Castillo-Duran C, Rodriguez A, Venegas G, Alvarez P, Icaza G. Zinc supplementation and growth of infants born small for gestational age. J Pediatr. 1995;127:206.
14. Osendrap SJ, Santosham M, Black RE, Wahed MA, Van Raaij JM, Fuchs GJ. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. Am J Clin Nutr. 2002;76:1401–8.
15. Friel JK, Andrews WL, Matthew JD, et al. Zinc supplementation in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr. 1993;17:97–104.
16. Sur D, Gupta DN, Mondal SK, et al. Impact of zinc supplementation on diarrhea morbidity and growth pattern of low birth weight infants in kolkata, India: a randomized, double-blind, placebo-controlled, community-based study. Pediatrics. 2003;112:1327–32.
17. Diaz-Gomez NM, Domenech E, Barroso F, Castells S, Cortabarria C, Jimenez A. The effect of zinc supplementation on linear growth, body composition, and growth factors in preterm infants. Pediatrics. 2003;111:1002–9.
18. Sur D, Mondal SK, Gupta DN, Ghosh S, Manna B, Sengupta PG. Impact of breastfeeding on weight gain and incidence of diarrhea among low birth weight infants of an urban slum of Calcutta. Indian Pediatr. 2001;38:381–4.
19. Prasad AS. Zinc deficiency in women, infants and children. J Am Coll Nutr. 1996;15:113–20.